Support for new Claims 73 and 74 is found throughout the specification, for example, in the claims as originally filed and in Figures 1A-1U. No new matter is added by the amendments.

Applicants submit that the amendments filed herein should be considered as they do not present new issues requiring further consideration or search.

Supplemental Information Disclosure Statement

Applicants note that a Supplemental Information Disclosure Statement was filed with Amendment A on February 19, 2003. Applicants request that the Examiner consider the Supplemental Information Disclosure Statement and return an initialed copy of it.

Rejection of Claims 1, 4-12, 14, and 17-18 Under 35 U.S.C. § 103(a)

Claims 1, 4-12, 14, and 17-18 stand rejected under 35 U.S.C. § 103(a) over Reinhard *et al.* (U.S. Patent No. 6,432,668 B1; hereafter "Reinhard"), or in the alternative Holmes *et al.* (U.S. Patent No. 5,403,717; hereafter "Holmes"), in view of Arnold *et al.* (U.S. Patent No. 6,423,535 B1; "hereafter "Arnold"). Specifically, the Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine and substitute a method wherein the gene expression profile is determined using the oligonucleotide arrays of Arnold and one or more equivalent genes (two intestinal polyp genes being taught by Reinhard and Holmes) responsible for intestinal polyps in the method of Reinhard or Holmes in order to achieve the express advantages noted by Arnold (*i.e.*, a method that provides quantitative information on each element of the microarray along with another advantage, hybridization of the probe sequence and the standard sequences being noncompetitive). Applicants respectfully disagree.

Reinhard discloses a human gene encoding a cyclin-dependent kinase named hPFTAIRE. Reinhard also discloses methods of diagnosing or prognosticating neoplasia in a mammal by measuring hPFTAIRE gene or protein expression in a first tissue suspected of being neoplastic and comparing it with hPFTAIRE gene or protein expression in a second normal tissue. Over-expression of the hPFTAIRE gene in the first tissue compared to the second tissue indicates neoplasia in the first tissue.

Holmes discloses diagnostic and prognostic methods for monitoring premalignant or malignant conditions of human secretory epithelia, for example, colonic epithelia, by determining the extent of expression of β1-3N-acetylglucosaminyltransferase.

Arnold discloses methods for normalizing and quantitating hybridization reactions by contacting distinct polynucleotide targets and standard polynucleotide targets with detectable nucleic acid probes complementary to the distinct targets and independently, detectable complements to the standard targets, to produce a hybridization pattern. The hybridization pattern is then detected and used to obtain information, including quantitative information, about the amount of polynucleotides in the sample. Arnold also discloses that the distinct and standard polynucleotide target can be attached to an array or a microarray and that the sample can be deposited on the array or microarray and hybridized to the probes.

Claim 1 recites a method of identifying an intestinal polyp comprising the steps of: a) obtaining a nucleic acid sample derived from intestinal tissue; and b) determining an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control, wherein increased expression of the nucleic acid molecules in the sample is indicative of an intestinal polyp. In addition, Claim 14 recites a method of identifying an intestinal polyp comprising the steps of: a) obtaining a polypeptide sample derived from intestinal tissue; and b) determining an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control, the expression products being polypeptides, wherein increased expression of the expression products in the sample is indicative of an intestinal polyp.

As stated in M.P.E.P. 2143, to establish a *prima facie* case of obviousness, three basic criteria are required: 1) there must be some suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. For the reasons set forth below, the combined references of Reinhard, or in the alternative Holmes, and Arnold do not meet these criteria, and thus do not render the claimed invention obvious.

The Combined References of Reinhard, Holmes, and Arnold Do Not Teach All of the Limitations of Claims 1, 4-12, 14, and 17-18

Reinhard discloses neoplasia diagnostic and prognostic methods by assessing the expression of only one nucleic acid molecule or one nucleic acid molecule product. Holmes discloses methods of diagnosing or prognosticating by assessing the expression of only one nucleic acid molecule or one nucleic acid molecule product. Neither of these references alone or combined, teach a method of identifying an intestinal polyp comprising determining an expression profile from expression products of at least three informative nucleic acid molecules.

Arnold does not compensate for the deficiencies of Reinhard and Holmes. In order for the methods of Claims 1 or 14 to be carried out, one must determine an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control. Therefore, one must know of three genes that are increased in an intestinal polyp relative to a control. Combined, Reinhard and Holmes do not teach three nucleic acid molecules with increased expression in an intestinal polyp. Arnold does not teach any methods for identifying an intestinal polyp or any nucleic acid molecules having increased expression in an intestinal polyp. Nor does Arnold teach how many informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control should be evaluated in order to determine an expression profile. Arnold's mere teaching of a method of quantitatively determining the amount of polynucleotides in a sample does not provide the additional information required for the method of Claims 1 or 14 to be performed. Thus, Applicants submit that the combined references of Reinhard, Holmes, and Arnold do not teach every limitation of Claims 1 or 14. In addition, Claims 4-12 depend from Claim 1, and Claims 17-18 depend from Claim 14, and are subject to all the limitations of Claims 1 and 14, respectively. Therefore the combined references of Reinhard, Holmes, and Arnold do not teach every element of these claims.

The Combined References of Reinhard, Holmes, and Arnold Do Not Provide a Suggestion or Motivation to Modify the References or Combine the Reference Teachings

Applicants submit that the combined references of Reinhard, Holmes, and Arnold do not provide a suggestion or motivation to modify or combine the teachings of the references to obtain the invention as recited in Claims 1, 4-12, 14, and 17-18. Neither Reinhard or Holmes suggests that expression levels of expression products other than the one gene disclosed in each respective

reference should be evaluated in order to identify intestinal polyps. Arnold does not make up for this deficiency; Arnold does not teach or suggest that an intestinal polyp can be identified using the described polynucleotide quantitation methods, nor does Arnold disclose three, two, or even one nucleic acid molecule that has increased expression in an intestinal polyp compared to a control. The statement by Arnold that his method provides quantitative information on each element of a microarray and that hybridization of the probe sequence and the standard sequence is non-competitive is not motivation to determine an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp, absent a teaching of the three nucleic acid molecules. Thus, neither Reinhard, Holmes, nor Arnold provide a suggestion or motivation to combine or modify any of the references to obtain the invention as recited in Claims 1, 4-12, 14, and 17-18.

In light of the above, Applicants submit that the teaching of Reinhard, Holmes, and Lees do not render the invention as recited in Claims 1, 4-12, 14, and 17-18 obvious. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 13 and 19 Under 35 U.S.C. § 103(a)

Claims 13 and 19 stand rejected under 35 U.S.C. § 103(a) over Reinhard, or in the alternative Holmes, in view of Arnold, further in view of Lee *et al.* (Hepatology 19(3):656-665, 1994; "hereafter "Lee"). The Examiner states that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method wherein one or more informative genes is selected from the group consisting of the genes in Figures 1A-1U of Lee in the method of Reinhard or in the alternative Holmes in view of Arnold, since Lee states that they found that the IGFBP-1 gene has several interesting potential regulatory sites and that IGFBP-1 mRNA and protein levels are increased in liver tissue and serum during liver regeneration. The Examiner further states that an ordinary practitioner would have been motivated to combine and substitute the method of Lee in the method of Reinhard or in the alternative Holmes in view of Arnold in order to achieve the express advantages noted by Lee (*i.e.*, a gene that has several interesting potential regulatory sites and the expression level of which is increased in liver tissue and serum during tissue damage). Applicants respectfully disagree.

Lee discloses the cloning and sequence analysis of the murine insulin-like growth factor binding protein-1 (IGFBP-1) gene. In addition, Lee discloses that IGFBP-1 mRNA and protein

levels are increased in liver tissue and serum during liver regeneration. Lee does not appear to teach that IGFBP-1 is expressed in intestinal tissue, nor does Lee teach or suggest that IGFBP-1 can be used to identify an intestinal polyp as recited in Claims 13 or 19.

Claim 13 depends from Clam 1 and recites a method of identifying an intestinal polyp comprising the steps of: a) obtaining a nucleic acid sample derived from intestinal tissue; and b) determining an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control, wherein one or more of the nucleic acid molecules is selected from the group consisting of the nucleic acid molecules in Figures 1A-1U, and wherein increased expression of the nucleic acid molecules in the sample is indicative of an intestinal polyp. Claim 19 depends from Claim 14 and recites a method of identifying an intestinal polyp comprising the steps of: a) obtaining a polypeptide sample derived from intestinal tissue; and b) determining an expression profile from expression products of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control, the expression products being polypeptides, wherein one or more of the nucleic acid molecules is selected from the group consisting of the nucleic acid molecules in Figures 1A-1U, and wherein increased expression of the expression products in the sample is indicative of an intestinal polyp.

As discussed above, Applicants assert that Claims 1 and 14 are not obvious in view of the combined teachings of Reinhard, Holmes, and Arnold. As Claims 13 and 19 depend from Claims 1 and 14, respectively, and are subject to all of the limitations of those claims, Applicants submit that Claims 13 and 19 are not obvious in view of Reinhard, Holmes, and Arnold. Applicants further contend that Lee does not compensate for the deficiencies of Reinhard, Holmes, and Arnold in satisfying the three basic criteria for establishing a *prima facie* case of obviousness. The IGFBP-1 gene cloned by Lee is listed as an informative nucleic acid molecule in Figures 1A-1U of the present application, but the data provided in Figures 1A-1U indicate that IGFBP is present in normal intestinal tissue and absent in intestinal polyps. Thus IGFBP-1 is not an informative nucleic acid molecule having increased expression in an intestinal polyp relative to a control as required by each of Claims 13 and 19. Accordingly, Applicants submit that the combined references of Reinhard, Holmes, Arnold, and Lee do not teach every limitation of Claims 13 and 19, which require determining the expression level of at least three informative nucleic acid molecules having increased expression in an intestinal polyp relative to a control.

Even assuming *arguendo* that the combined references did teach every element, the combined references do not provide a suggestion or motivation to modify or combine the teachings of the references to obtain the invention as recited in Claims 13 or 19. Neither Reinhard nor Holmes teach or suggest that any additional genes other than the one gene disclosed in each respective reference should be evaluated in order to identify an intestinal polyp, and they do not suggest that at least three informative nucleic acid molecules selected from the nucleic acid molecules in Figures 1A-1U should be examined, as recited in Claims 13 and 19. Arnold does not teach or suggest any informative genes that can be used to identify an intestinal polyp as recited in Claims 13 and 19. And Lee does not teach or suggest that the IGFBP-1 gene is expressed in intestinal tissue or that the IGFBP-1 gene has increased expression in intestinal polyps relative to normal tissue. In addition, Lee does not teach or suggest that the IGFBP-1 gene can be used to identify an intestinal polyp according to the methods of Claims 13 or 19. Thus, the combination of Reinhard, Holmes, Arnold and Lee provides no suggestion or motivation to combine or modify any of the references to obtain the invention as recited in Claims 13 or 19.

Support for new Claims 73 and 74 is found throughout the specification, for example, in the claims as originally filed and in Figures 1A-1U.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Karen J. Townsend

Karen J. Townsend
Registration No. 50,675
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: June 25, 2003